Claims

1. A controlled release formulation containing galantamine as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating.

2. A formulation according to claim 1 wherein galantamine is in the form of galantamine hydrobromide (1:1).

3. A formulation according to claim 1 wherein the water soluble excipient is a film forming polymer.

4. A formulation according to claim 3 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution.

5. A formulation according to claim 4 wherein the water soluble polymer is selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose,
- hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectines such as sodium carboxymethylamylopectine,
- chitine derivates such as chitosan,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,

- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

6. A formulation according to claim 5 wherein the water soluble polymer is hydroxypropyl methylcellulose HPMC 2910 5 mPa.s.

7. A formulation according to claim 6 wherein the weight-by-weight ratio of hydroxypropyl methylcellulose HPMC 2910 5 mPa.s to galantamine is in the range of 17 : 1 to 1 : 5.

8. A formulation according to claim 2 wherein galantamine hydrobromide (1:1) and the water soluble, film forming polymer are layered or coated on an inert sphere.

9. A formulation according to claim 8 wherein the inert spheres are 16-60 mesh (1,180-250 • m) sugar spheres (NF XVII, page 1989).

10. A formulation according to claim 1 wherein the release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer.

11. A formulation according to claim 10 wherein the water insoluble polymer is ethylcellulose and the plasticizer is selected from the group comprising dibutyl sebacate, diethyl phthalate and triethyl citrate.

12. A formulation according to claim 11 wherein the weight of the release rate controlling membrane coating ranges from 3 % to 15 % of the uncoated particle.

13. A formulation according to claim 1 wherein a seal coat lies between the drug core and the release rate controlling membrane coating.

14. A formulation according to any one of claims 1 to 13 further comprising a topcoat comprising galantamine and water-soluble polymer.

15. A formulation according to claim 14 capable of releasing in USP buffer pH 6.8 at 37°C in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791-1793, paddle, 50

rpm) from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours

16. A dosage form comprising a therapeutically effective amount of the controlled release formulation of any of claims 1 to 15.

17. A dosage form according to claim 16 which delivers a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.

18. A dosage form according to claim 16 wherein part of the galantamine is present in an immediate release form.

19. A dosage form according to claim 18 wherein said immediate release form comprises particles as described in claim 1 lacking the release rate controlling membrane.

20. A dosage form according to claim 18 wherein said immediate release form comprises immediate release minitablets.

21. A dosage form according to claim 18 wherein said immediate release form comprises a controlled release formulation of claim 14.

22. A dosage form according to claim 16 providing a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.

23. A pharmaceutical package suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.

24. A pharmaceutical package as claimed in claim 23 adapted for titrating a patient who is 'acetylcholine esterase inhibitor'-naïve, characterized in that said package comprises 21-35 daily sequential dosage units of
(a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine,
(b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine,

(c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and

(d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.

25. A pharmaceutical package as claimed in claim 23 adapted for treating a patient who is 'acetylcholine esterase inhibitor'-tolerant, characterized in that said package comprises daily dosage units comprising from 15 to 30 mg galantamine.

26. A process of preparing a formulation according to claim 1 comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.

27. A method of treating Alzheimer's dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia and related dementias, but insufficient to cause said adverse effects.

28. A method accoring to claim 27 wherein the related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficiet, hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.

29. A method according to claim 27 wherein the adverse effects belong to the group comprising nausea, vomiting, sweating, restlessness, and insomnia.